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Causal Associations Between Sleep Traits and Delirium: A Bidirectional Two-Sample Mendelian Randomization Study

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Purpose: Numerous studies have identified a correlation between sleep and delirium; however, the causal relationship remains ambiguous. This bidirectional two-sample Mendelian randomization (MR) study was conducted to examine the possible causal relationships between sleep traits and delirium.

Patients and Methods: Utilizing genome-wide association studies (GWAS), we identified ten sleep traits: chronotype, sleep duration, short sleep duration, long sleep duration, daytime napping, daytime sleepiness, insomnia, number of sleep episodes (NSE), sleep efficiency, and rapid eye movement sleep behavior disorder (RBD). In this MR study, genetic variants independently associated with exposures were selected as instrumental variables (IVs). To establish causal inferences, three regression models were employed—inverse variance weighted (IVW), MR Egger, and weighted median (WM) —and conducted sensitivity analyses to assess the robustness of our findings.

Results: Our results suggest no significant causal association between the ten sleep traits and the risk of delirium. The reverse MR analysis revealed that delirium is associated with an increased propensity for morning chronotype [OR_{IVW}, 1.025; 95% CI, 1.012–1.036; p = 1.50E-05; adjusted p values ($p_{adjusted}$)= 1.35E-04] and a decreased risk of long sleep duration [OR_{IVW}, 0.996; 95% CI, 0.993–0.999; p = 0.013; $p_{adjusted}$= 0.059]. However, no robust evidence currently exists to substantiate a causal relationship between delirium and other sleep traits.

Conclusion: Our bidirectional, two-sample MR analysis study did not provide definitive evidence that sleep traits may augment the susceptibility to delirium. However, the reverse MR results indicate that delirium may predispose patients to an earlier sleep-wake cycle. Additional large-scale investigations are necessary to examine the bidirectional causality between delirium and sleep traits.

Keywords: sleep traits, delirium, Mendelian randomization analysis, genome-wide association studies

Introduction

Delirium is a cognitive disorder characterized by sudden, fluctuating disturbances in attention and awareness.[1] Postoperative delirium typically manifests between the second and fifth postoperative days. Although it occurs in only 2–3% of the general surgical population, it has been reported in up to 50–70% of high-risk patient groups.[2,3] It affects not only the patient's cognitive function and quality of life[4] but is also associated with significantly higher morbidity and mortality.[1] Therefore, it is considered a significant health concern due to its potential to cause various short-term and long-term negative effects.

Although the etiology of delirium is not well known, evidence suggests a possible association between sleep disorders and delirium.[5] Sleep quality and disruptions are currently receiving significant interest in the field of delirium research.[6]

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The sleep patterns of individuals with delirium are characterized by short duration of rapid eye movement sleep and poor quality of sleep.[7] Evidence indicates that individuals with a history of sleep disorders have a fivefold increased risk of experiencing postoperative delirium compared to those without such conditions.[8] Synthesizing the results of numerous studies demonstrated significant associations between certain sleep traits and delirium[4] and suggested that sleep disturbances could be a modifiable risk factor for delirium.[9,10] Additionally, since sleep disorders often coexist with delirium[11] and share common pathophysiological pathways and mechanisms,[12] it remains unclear whether sleep disturbances are a cause of delirium or a consequence.[13,14] Some researchers believe that the relationship between sleep and delirium is bidirectional.[5,15] Nevertheless, due to the lack of specific sleep trait categorizations and the susceptibility of published studies to confounding variables, elucidating the causal association between sleep and delirium remains challenging. Conducting randomized trials that encompass all categories of sleep traits in real-world settings is equally challenging.

We extensively reviewed published GWAS and related literature to comprehensively evaluate the association between various sleep traits and delirium, ultimately identifying ten specific sleep traits. These traits include chronotype, sleep duration, long sleep duration, short sleep duration, daytime napping, daytime sleepiness, insomnia, NSE, sleep efficiency, and RBD. Meanwhile, MR, a burgeoning epidemiological methodology, uses genetic variants independently associated with exposure as IVs to assess causality between exposures and outcomes. Because genetic variants are randomly assigned at conception, MR analyses are not influenced by environmental confounders. Furthermore, since disease onset and progression do not alter fixed alleles, MR helps avoid bias from reverse causation in the results.[16] Therefore, using MR, we can obtain more robust causal inferences regarding the relationship between sleep traits and delirium.

Methods

Study Design

The causal association between ten sleep traits and delirium was assessed by a bidirectional two-sample MR study utilizing data from GWAS. Three primary assumptions underlie the MR study: (1) the assumption of relevance: IVs should have a strong association with the exposure; (2) the assumption of exclusivity: IVs should not have a direct relationship on the outcome other than through the exposure; and (3) the assumption of independence: IV should not be associated with any confounding factors that may influence the causal relationship (Figure 1). [17,18]

Data Sources

Among the ten sleep traits, RBD data were obtained from the GWAS Catalog. The UK Biobank provided the GWAS data for the remaining sleep traits, currently accessible through the Sleep Disorder Knowledge Portal. The UK Biobank, an extensive population-based research, was established to enable thorough examinations of the genetic and lifestyle factors influencing a wide array of phenotypes.[6] From 2006 to 2010, over 500,000 individuals aged 40–69 and residing within a 25-mile radius of the research center in the United Kingdom were included in the study. GWAS data for delirium were obtained from the FinnGen Consortium (https://r11.finngen.fi/pheno/F5_DELIRIUM). The FinnGen Consortium is an extensive biomedical research initiative conducted in Finland. Its primary objective is to identify novel biomarkers and therapeutic targets through the analysis of genetic data and medical data of Finnish volunteers.

Detailed information regarding the ten sleep traits[19–25] and delirium included in this study is presented in Table 1. Additionally, the participants in the datasets utilized for the MR analysis were predominantly individuals of European descent. Given that the data were derived from published studies, ethical approval and informed consent were not required.

Selection of IVs

We rigorously selected IVs following the steps below. Initially, single nucleotide polymorphisms (SNPs) significantly associated with exposure (significance threshold: $p < 5\times10^{-8}$) were selected. To prevent co-linearity among SNPs, we established the linkage disequilibrium threshold (r^2) at 0.001 and ensured the independence of each SNP by setting the clumping window to 10 MB.[26] If the number of SNPs examined was insufficient, we modified the threshold to $p < 5\times10^{-6}$. The F-statistic was then employed to evaluate the strength of the association between the IVs and the exposure.

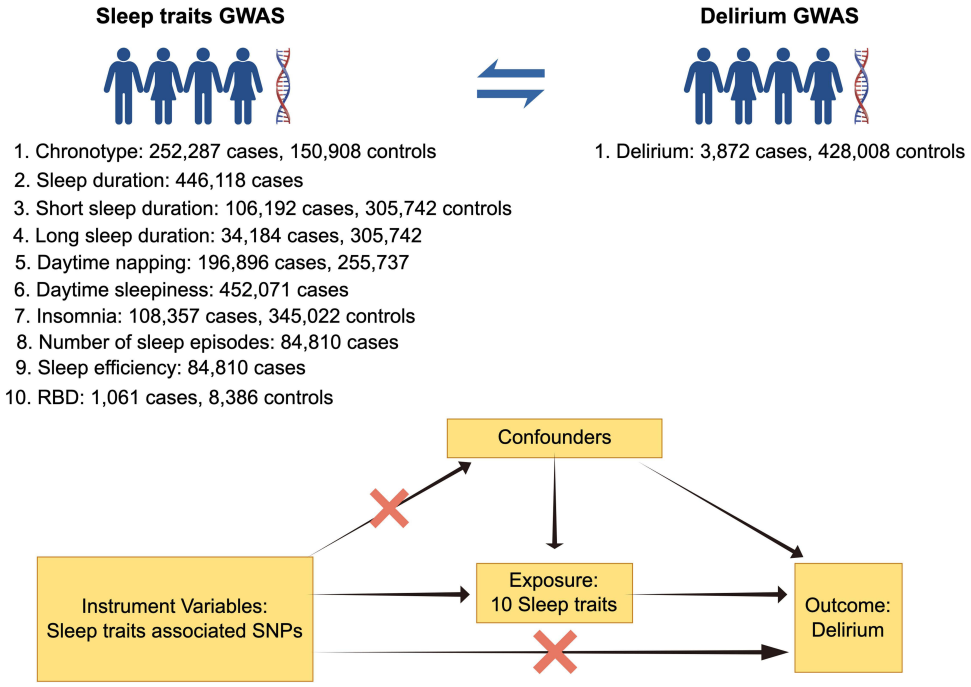

Figure 1 MR model of exposure and risk of delirium. The design of this study was based on the following hypotheses: genetic variants are associated with exposure but not with confounders; genetic variants affect delirium only through exposure.

IVs were considered robust, and MR results were unlikely to be affected by weak IV when the F statistic was greater than 10. Conversely, IVs were excluded if the F statistic was less than 10. Then, We utilized online data from the GWAS Catalog and the LDlink dataset[27,28] to remove SNPs associated with confounding factors such as neuroticism, diabetes, and cognitive impairment.[29] Finally, we harmonized the data between $SNP_{exposure}$ and $SNP_{outcome}$.

Table 1 Detailed Information Regarding the ten Sleep Traits and Delirium Included in This Study

Sleep Traits (Type of Trait)	Definition (Sample Size)	Author, Published Year	Case Group	Control Group	Consortium PMID
Chronotype (Binary)	The chronotype refers to an individual's natural inclination toward earlier or later sleep times. (N = 403,195)	Jones SE et al, 2019	Morning Chronotype (N =252, 287): individuals who go to bed early and rise early.	Evening Chronotype (N= 150, 908): individuals who go to bed late and rise late.	UKB 30696823
Sleep duration (Continuous)	The average duration of sleep obtained in a 24-hour period, including nap times. (N = 446,118)	Dashti HS et al, 2019	-	-	UKB 30846698
Short sleep duration (Binary)	The average duration of sleep obtained in a 24-hour period, including nap times. (N = 411,934)	Dashti HS et al, 2019	Short sleep duration (N = 106,192): ≤6 hours of sleep per 24 hours.	Normal sleep duration (N = 305,742): 7–8 hours of sleep per 24 hours.	UKB 30846698
Long sleep duration (Binary)	The average duration of sleep they get each 24-hour period, taking into account nap times. (N = 39,926)	Dashti HS et al, 2019	Long sleep duration (N = 34,184): ≥9 hours of sleep per 24 hours.	Normal sleep duration (N = 305,742): 7–8 hours of sleep per 24 hours.	UKB 30846698

(*Continued*)

Table 1 (Continued).

Sleep Traits (Type of Trait)	Definition (Sample Size)	Author, Published Year	Case Group	Control Group	Consortium PMID
Daytime napping (Binary)	Self-reported frequency of daytime naps: "Do you take naps during the day?" (N = 452,633)	Dashti HS et al, 2021	Occasionally and always (N = 196,896)	Never and rarely (N = 255,737)	UKB 33568662
Daytime sleepiness (Continuous)	Likelihood of dozing off or falling asleep during the daytime when unintended. (N = 452,071)	Wang H et al, 2019	-	-	UKB 31409809
Insomnia (Binary)	Self-reported difficulty in falling asleep at night or frequent awakenings during the night.	Lane JM et al, 2019	Sometimes/usually (N = 108,357)	Never/rarely (N = 345,022)	UKB 30804565
NSE (Continuous)	Measured using a triaxial accelerometer (Axivity AX3) worn continuously for up to 7 days post-baseline. (N = 84,810)	Jones SE et al, 2019	-	-	UKB 30952852
Sleep efficiency (Continuous)	Measured using a triaxial accelerometer (Axivity AX3) worn continuously for up to 7 days post-baseline. Calculated as the ratio of total sleep duration to the time between the start of the first and end of the last nocturnal inactivity period (N= 84,810)	Jones SE et al, 2019	-	-	UKB 30952852
RBD (Binary)	Defined as the loss of muscle atonia and enactment of dreams during REM sleep.	Krohn L et al, 2022	Case group (N = 1,061)	Control group (N = 8,386)	GWAS catalog 36470867
Delirium (Binary)	Delirium not related to alcohol or other psychotropic substances. (N = 431,880)	NA	Case group (N = 3,827)	Control group (N = 428,053)	FinnGen -

Abbreviations: NSE, Number of sleep episodes; RBD, Rapid-eye-movement sleep behavior disorder.

MR Analysis

A two-sample MR analysis was conducted to assess the causal relationship between sleep traits and delirium. The MR analyses primarily employed IVW to assess causality. Additionally, MR Egger and WM were utilized as a complementary analytical approach to assess the consistency of the causal estimates. IVW is characterized by omitting the intercept term and weighting the data by the inverse of the outcome variance to optimize the fit.[30] In contrast to IVW, MR Egger includes an intercept term in its regression model while also weighting data by the inverse of the outcome variance to improve the fit.[31] WM calculates the median effect estimate of the distribution function by ranking all SNP effect values based on their weights. It offers robust estimates of causal effects, even when up to 50% of the IVs are null.[32] For inference of final causal inferences, it is necessary to satisfy the $p < 0.05$ in the IVW test along with the following conditions: (1) Either MR Egger or WM test shows a $p < 0.05$. (2) the ORs of the IVW and the WM consistently indicate that the effect is in the same direction. (3) No statistically significant evidence of horizontal pleiotropy is detected ($p > 0.05$). (4) In the leave-one-out analysis, all error bars consistently remained on one side of zero. (5) These criteria remain valid even after adjusting for heterogeneity. At last, the p value of the IVW was modified by considering the false detection rate (FDR).[33] This MR study followed the Strengthening the Reporting of Observational Studies in Epidemiology using MR (STROBE-MR) (Supplementary Figure 1).[34] All analyses were conducted using R software (version 4.4.0) incorporating the TwoSampleMR and MR-PRESSO packages.

Sensitivity Analysis

To assess potential violations of the MR assumptions, we conducted sensitivity analyses using Cochran's Q test, MR-Egger intercept, MR PRESSO test, and leave-one-out method to evaluate the stability and reliability of the results. We used Cochran's Q test to assess the degree of heterogeneity. When significant heterogeneity was detected, a random effects model was used; otherwise, a fixed effects model was applied.[35] The MR-Egger intercept and MR PRESSO test were used to assess the presence of horizontal pleiotropy, while the MR PRESSO global was used to identify potential outliers. If the test results indicated the presence of horizontal pleiotropy or outliers, we adjusted the MR analysis by excluding the outliers. Finally, a leave-one-out analysis was conducted to remove each SNP individually to assess the combined effect of the remaining SNPs. All error lines consistently remained on the side of zero, indicating the results were reliable.

Results

Results of IV Selection

Based on the described process, we identified all IVs for the exposures (Supplementary Tables).1–11 Among them, when examining the effects of insomnia, RBD, and sleep efficiency on delirium, as well as the effects of delirium on sleep traits, we applied a less stringent significance threshold ($p < 5\times10^{-6}$) to extract sufficient accounts of SNPs. Moreover, we calculated the F statistic for each SNP (Supplementary Tables 1–11), and the F statistic for each exposure (Supplementary Table 12). Weak IVs are unlikely to affect the MR results, as the F statistic for each SNP exceeds 10.

Effect of Sleep Traits on Delirium

No causal relationship was identified between the ten sleep traits and delirium when we these sleep traits were used as exposures (Figure 2 and Supplementary Figures).2–5.

Exposure	Outcome	No.SNPs	Method	OR (95% CI)	P−Value	Adjusted−P−Value
Chronotype	Delirium	143	Inverse variance weighted	0.886 (0.711 to 1.104)	0.279	0.635
			Weighted median	0.872 (0.643 to 1.183)	0.380	
			MR Egger	0.831 (0.418 to 1.652)	0.599	
Daytime napping	Delirium	89	Inverse variance weighted	0.882 (0.490 to 1.587)	0.675	0.687
			Weighted median	1.523 (0.627 to 3.700)	0.353	
			MR Egger	1.333 (0.159 to 11.150)	0.791	
Daytime sleepiness	Delirium	36	Inverse variance weighted	0.750 (0.209 to 2.695)	0.659	0.687
			Weighted median	0.371 (0.062 to 2.240)	0.280	
			MR Egger	1.397 (0.005 to 396.417)	0.908	
Insomnia	Delirium	36	Inverse variance weighted	1.496 (0.607 to 3.687)	0.381	0.635
			Weighted median	1.083 (0.272 to 4.310)	0.909	
			MR Egger	2.253 (0.147 to 34.504)	0.564	
Long sleep duration	Delirium	9	Inverse variance weighted	18.293 (0.295 to 1133.383)	0.167	0.635
			Weighted median	48.010 (0.182 to 12671.128)	0.174	
			MR Egger	28.621 (0.000 to 22145326.130)	0.643	
Number of sleep episodes	Delirium	19	Inverse variance weighted	1.051 (0.951 to 1.161)	0.329	0.635
			Weighted median	1.055 (0.922 to 1.207)	0.435	
			MR Egger	0.929 (0.573 to 1.507)	0.770	
Short sleep duration	Delirium	23	Inverse variance weighted	1.484 (0.217 to 10.147)	0.687	0.687
			Weighted median	1.791 (0.157 to 20.396)	0.639	
			MR Egger	0.002 (0.000 to 69.301)	0.257	
RBD	Delirium	49	Inverse variance weighted	0.989 (0.971 to 1.007)	0.230	0.635
			Weighted median	0.993 (0.967 to 1.020)	0.617	
			MR Egger	0.980 (0.951 to 1.010)	0.197	
Sleep duration	Delirium	64	Inverse variance weighted	1.223 (0.782 to 1.911)	0.378	0.635
			Weighted median	0.782 (0.414 to 1.480)	0.450	
			MR Egger	1.191 (0.210 to 6.753)	0.844	
Sleep efficiency	Delirium	33	Inverse variance weighted	4.098 (0.057 to 296.935)	0.519	0.687
			Weighted median	3.967 (0.006 to 2442.324)	0.674	
			MR Egger	0.002 (0.000 to 19.712)	0.191	

Figure 2 Forest plots utilized Three methods to visualize the causal effects of Sleep traits on Delirium risk.

Effect of Delirium on Sleep Traits

Delirium may be a risk factor for morning chronotype when considered as the exposure variable [OR_{IVW}, 1.025; 95% CI, 1.012–1.036; p = 1.50E-05; adjusted p values ($p_{adjusted}$)= 1.35E-04]. Conversely, the association between delirium and long sleep duration was not statistically significant after adjustment [OR_{IVW}, 0.996; 95% CI, 0.993–0.999; p = 0.013; $p_{adjusted}$= 0.059] (Figure 3). Furthermore, when estimating the effect of delirium on insomnia, no outcome variable corresponding to the IV for delirium was identified. Ultimately, we were unable to establish a causality between delirium and the remaining sleep traits. (Figure 3 and Supplementary Figures).6–8.

Results of Sensitivity Analysis

We observed significant heterogeneity in the effects of insomnia, NSE, and short sleep duration on delirium. Similarly, reverse MR analysis revealed substantial heterogeneity in the impact of delirium on daytime napping, NSE, short sleep duration, and sleep duration (Q-pval < 0.05). The MR-Egger intercept test did not detect horizontal pleiotropy; however, the MR-PRESSO test detected significant horizontal pleiotropy between insomnia, the NSE, short sleep duration, and delirium, as well as between delirium and daytime napping. Therefore, we reanalyzed after removing the outlier SNPs detected: rs7711696, rs429358, rs4585442, and rs1831043—which effectively mitigated pleiotropy and heterogeneity (Supplementary Table 14). Furthermore, we performed leave-one-out analyses, displaying the results in Figure 4 and Supplementary Figures .1–7.

Discussions

This study employed MR analysis to investigate the bidirectional causality between ten sleep traits and delirium. Gene prediction results indicated that none of the ten sleep traits serve as risk factors for delirium; rather, delirium may increase the risk of morning chronotype and decrease the likelihood of long sleep duration. This suggests that delirium may predispose patients to an earlier sleep-wake cycle, with a total sleep duration unlikely to exceed nine hours within a 24-hour period. Our findings provide strong support for a potential bidirectional causal relationship between delirium and sleep. However, at present, there is a lack of theoretical foundation elucidating the pathophysiological mechanisms

Exposure	Outcome	No.SNPs	Method	OR (95% CI)	P−Value	Adjusted−P−Value
Delirium	Chronotype	9	Inverse variance weighted	1.025 (1.013 to 1.036)	1.50E-05	1.35E-04
			Weighted median	1.026 (1.010 to 1.042)	0.001	
			MR Egger	1.035 (1.015 to 1.055)	0.010	
Delirium	Daytime napping	7	Inverse variance weighted	1.001 (0.993 to 1.009)	0.801	0.956
			Weighted median	1.003 (0.993 to 1.013)	0.536	
			MR Egger	1.005 (0.989 to 1.021)	0.596	
Delirium	Daytime sleepiness	9	Inverse variance weighted	1.000 (0.996 to 1.004)	0.948	0.956
			Weighted median	0.999 (0.993 to 1.004)	0.601	
			MR Egger	1.000 (0.993 to 1.008)	0.911	
Delirium	Long sleep duration	9	Inverse variance weighted	0.996 (0.993 to 0.999)	0.013	0.059
			Weighted median	0.996 (0.992 to 1.000)	0.046	
			MR Egger	0.997 (0.991 to 1.003)	0.413	
Delirium	Number of sleep episodes	8	Inverse variance weighted	1.003 (0.910 to 1.105)	0.956	0.956
			Weighted median	1.000 (0.882 to 1.134)	0.999	
			MR Egger	0.933 (0.774 to 1.124)	0.491	
Delirium	Short sleep duration	9	Inverse variance weighted	1.002 (0.996 to 1.008)	0.550	0.956
			Weighted median	1.001 (0.996 to 1.006)	0.699	
			MR Egger	1.005 (0.994 to 1.016)	0.421	
Delirium	RBD	9	Inverse variance weighted	1.053 (0.841 to 1.318)	0.655	0.956
			Weighted median	1.073 (0.805 to 1.429)	0.631	
			MR Egger	1.100 (0.737 to 1.642)	0.654	
Delirium	Sleep duration	9	Inverse variance weighted	0.989 (0.976 to 1.001)	0.082	0.246
			Weighted median	0.986 (0.973 to 1.000)	0.042	
			MR Egger	0.985 (0.962 to 1.009)	0.268	
Delirium	Sleep efficiency	9	Inverse variance weighted	1.000 (0.999 to 1.002)	0.690	0.956
			Weighted median	1.000 (0.998 to 1.002)	0.891	
			MR Egger	1.000 (0.998 to 1.003)	0.765	

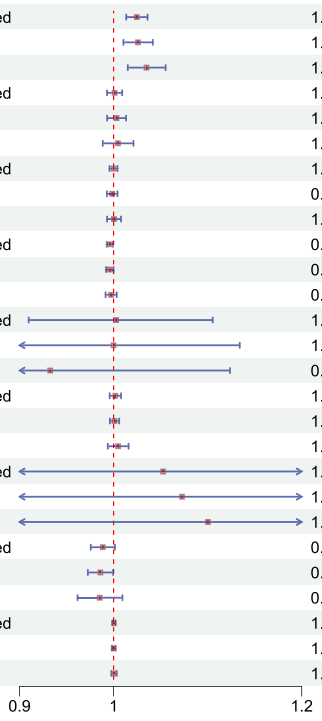

Figure 3 Forest plots utilized Three methods to visualize the causal effects of Delirium on Sleep traits risk.

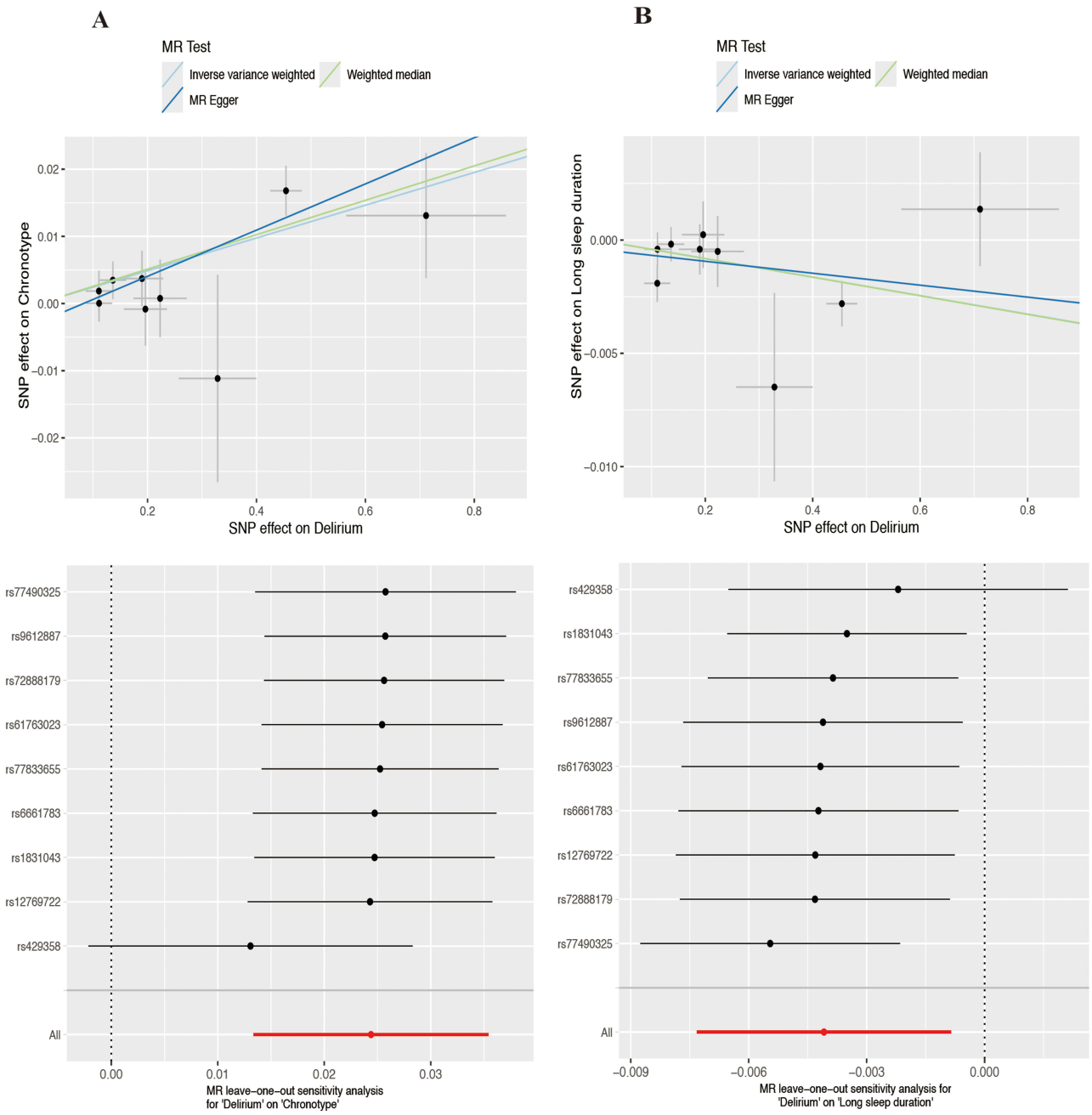

Figure 4 Visualization of the MR analysis of the effect of Delirium on Chronotype and Long sleep duration. (**A**) Scatter plot of the MR analysis and Leave-one-out sensitivity analysis of the effect of Delirium on Chronotype; (**B**) Scatter plot of the MR analysis and Leave-one-out sensitivity analysis of the effect of Delirium on Long sleep duration.

by which delirium influences sleep, as current research primarily focuses on the effects of sleep on delirium[36–38] while neglecting the impact of delirium on sleep. Consequently, further research is necessary to supplement and elucidate the existing findings.

Our results contradict some of the previous findings regarding sleep and delirium. On the one hand, a prospective study using postoperative sleep and electroencephalograms to predict postoperative delirium showed that sleep deprivation on the first night after surgery was an early predictor of postoperative delirium.[39] Several meta-analyses have also demonstrated a significant correlation between sleep disorders,[8] sleep disruption,[9] and insomnia in emergency situations[40] and the incidence of delirium. On the other hand, drugs used for sleep interventions, such as dexmedetomidine[41,42] and melatonin[43,44] have been observed to be effective in preventing delirium. Dexmedetomidine

effectively maintains normal sleep structure due to the spindle waves and slow delta oscillation it generates, which are in close proximity to the N2 sleep stage. Consequently, sleep efficacy is improved, and subjective sleep quality is optimized.[45] Melatonin regulates sleep patterns, and maintaining circadian rhythms has been shown to be effective in preventing delirium.[46] In summary, these evidence suggests a potential causality between sleep and delirium.

Nevertheless, our results did not demonstrate that specific sleep traits are directly causally associated with an increased risk of delirium. However, we do not discount the influence of sleep on delirium. We consider that sleep may raise the susceptibility to delirium through indirect pathways. Previous research has indicated a bidirectional association between sleep disorders and depression,[47] meaning that sleep may heighten the likelihood of depression, while major depression may lead to an increased risk of delirium. Similarly, recent MR studies have found that insomnia, daytime napping, and sleep apnea syndrome are positively correlated with frailty index.[48] Furthermore, there is a robust correlation between the frailty index and a higher likelihood of experiencing delirium.[49] Additionally, an MR study of sleep traits and gut microbiota revealed that daytime napping could elevate the proportion of the microbial family Desulfovibrionaceae,[50] and that the presence of these bacteria may increase the risk of delirium.[51] This leads us to speculate that sleep could indirectly increase the risk of delirium through factors such as depression, frailty index, and gut microbiota. This hypothesis needs to be confirmed by further studies.

Failure to differentiate subtypes of delirium is an additional potential factor contributing to contradictory findings between our bidirectional MR analysis and those of prior studies. The most commonly used classification criterion, based on psychomotor signs, divides delirium into three main categories: hypoactive, hyperactive, and mixed.[52] Hypoactive delirium is the predominant form and is characterized by reduced psychomotor activity, lethargy, and increased GABA and melatonin activity.[53] The symptoms of hyperactive delirium include heightened psychomotor activity, restlessness, disruptive behavior, sleep-wake disturbances, and hallucinations.[54] Patients suffering from mixed delirium experience oscillations between either hypoactive or hyperactive states. Although delirium caused by alcohol consumption was excluded from the GWAS data used in this study, no details of the subtypes of the included delirium population were provided. This lack of detailed data may have introduced bias into our results due to the wide disparity or even complete opposition of sleep traits among the different subtypes. To address this issue, we attempted to find GWAS data that included differentiated delirium subtypes; however, after a comprehensive search, no data meeting our criteria were found.

To the best of our knowledge, this is the first study to apply MR methodology to explore the bidirectional causality between ten sleep traits and delirium. This research significantly expands the existing research in this area. Meanwhile, MR analysis is less susceptible to confounding factors, effectively reduces the possibility of confounding bias, and can provide more reliable causal inference results. Nevertheless, certain limitations exist in our study. Firstly, we need to further investigate whether we can extrapolate the results to populations of other origins, given that the GWAS datasets are all of European origin. Second, this study primarily obtained the GWAS data for some sleep traits through self-reported questionnaires rather than objective measurements, which could potentially bias the results.

Conclusions

In summary, our bidirectional, two-sample MR analysis study did not provide conclusive evidence that sleep traits may increase susceptibility to delirium. However, the reverse MR results indicate that delirium may predispose patients to an earlier sleep-wake cycle. Additional large-scale investigations are necessary to examine the bidirectional causality between delirium and sleep traits.

Abbreviations

GWAS, Genome-wide association studies; IV, Instrumental variable; IVW, Inverse variance weighted; MR, Mendelian randomization; NSE, Number of sleep episodes; RBD, Rapid eye movement sleep behavior disorder; SNP, Single nucleotide polymorphism; WM, Weighted median.

Data Sharing Statement

Please refer to the article and Supplementary Materials for the comprehensive datasets and GWAS data sources. Should you require any information, do reach out to the corresponding author.

Ethics Approval

The data used in this study are sourced from publicly available large-scale GWAS, with ethical approval and informed consent obtained in the original studies. Consequently, this study aligns with the exemption approval policy of the Ethics Committee of Guangzhou University of Chinese Medicine and has been granted exemption approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors claim that the research had no commercial or financial conflicts of interest.

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